Comparative Efficacy and Procedural Durability of Radiofrequency Ablation for Atrial Fibrillation: A Systematic Review and a Meta-Analysis

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Objectives: In patients with atrial fibrillation (AF), the success rate of pulmonary vein isolation procedure has improved with advances in three-dimensional mapping systems but procedure remains complex and time-consuming. AF ablation using a multielectrode catheters enabling both mapping and ablation have been developed to address the technical difficulties. Our objective was to systematically review current knowledge on the efficacy and procedural durability of AF ablation using a multielectrode catheter (MEA), compared to conventional pulmonary vein isolation (CPVI). **Methods:** We systematically searched PubMed, EMBASE, Cochrane, and Korean domestic databases for studies on MEA and CPVI. **Results:** Our meta-analysis showed that procedural time [standardized mean difference (SMD)=-1.17, 95% confidence interval (CI): -1.67, -0.67] and fluoroscopic time (SMD=-0.64, 95% CI: -1.04, -0.24) were significantly shorter in MEA. The risk of AF recurrence [relative risk (RR)=0.85, 95% CI: 0.76, 0.94] was significantly lower and repeat procedures (RR=0.73, 95% CI: 0.53, 1.00) tended to be lower in MEA without statistical significance. No significant between-treatment difference in complication rates was evident with a trend toward higher complication rate in MEA (RR=1.04, 95% CI: 0.55, 1.93). **Conclusion:** In patients undergoing catheter ablation to treat AF, the efficacies of MEA and CPVI were comparable in terms of acute procedural success and repeat procedures. However, MEA afforded the benefit of reduced procedure-related time, including procedural time, fluoroscopic time, and radiofrequency application time and lower AF recurrence. MEA was associated with a slightly higher risk of thromboembolism, but nonetheless afforded patient benefits, when skilled physicians carefully performed all procedures.

Key Words Atrial fibrillation · Catheter ablation · Multielectrode ablation · Conventional pulmonary vein ablation · Radiofrequency ablation · Meta-analysis.

Introduction

Atrial fibrillation (AF) is triggered by ectopic beating of the pulmonary vein (PV), and catheter-based pulmonary vein isolation (PVI) using radiofrequency is accepted to be effective for treatment of patients in whom AF is refractory to anti-arrhythmic drugs.[1,2] The preferred ablation strategy features electrical isolation of the PV by creation of circumferential lesions around the right and left PV ostia.[3] Although three-dimensional (3D) mapping systems are routinely used for catheter-based PVI, point-by-point ablation remains complex and time-consuming, requiring a high level of technical competence. Such technical complexity and the need to visualize the circular mapping and ablation catheters in real time, means that many centers perform only one or two procedures daily, and patients endure long-term procedural discomfort and are exposed to the risks associated with general anesthesia. More importantly, patients are subjected to significant levels of radiation (shared to some extent by the operators).[4-7] The adverse effects of radiation exposure during the catheter ablation are well documented in medical literature.[8,9] To address such technical difficulties; and to render the procedure simpler, shorter, and safer; multielectrode catheters enabling simultaneous mapping and ablation have been developed. Such catheters allow an operator to create lesions over much of the circumference of each PV via a single radiofrequency (RF) application, without

having to change position. Thus, procedural time is reduced; the need for fluoroscopy minimized; procedural efficacy and safety maintained or improved; and AF ablation rendered more accessible, associated with shorter surgical learning curves.[10]

To date, only three systematic reviews on the use of catheter-based ablation to treat AF have appeared, of which two compared catheter ablation with medical treatment.[11,12] One review assessed the safety and efficacy of AF ablation using phased RF energy and multielectrode catheters, but presented only quantitative acute procedural and 6/12 month success rates.[13]

No previous study has systematically reviewed the efficacy and safety of multielectrode catheter ablation (MEA) compared to conventional PV isolation (CPVI). Therefore, the objective of our present study was to systematically review the efficacy and procedural durability of AF ablation using multielectrode catheters (the MEA procedure), and CPVI.

Methods

We systematically reviewed available data using a predetermined protocol established by reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (http://www.prisma-statement.org/).

Search strategy

To identify and retrieve all relevant literature describing the outcomes of AF patients treated via MEA, we searched PubMed, EMBASE, Cochrane, and four Korean domestic databases in April 2015. Search terms included both keywords and corresponding Medical Subject Headings; thus "atrial fibrillation" AND "multielectrode radiofrequency ablation" AND "conventional point-by-point ablation". Inclusion criteria were: 1) the work was an original article on AF patients; 2) the research design was controlled; 3) MEA was compared with conventional ablation using 3D mapping methods; and, 4) the language of publication was English or Korean. Exclusion criteria were: 1) research on conditions other than paroxysmal or persistent AF; 2) treatment with other than MEA; 3) comparison of MEA with conditions other than CPVI; 4) non-reporting of MEA outcomes reported; 5) non-reporting of MEA efficacy; 6) a case series or a case report; 7) an animal study or an abstract-only publication; and, 8) an evidence level lower than two upon analysis of bias risk. Secondary texts were identified via manual review of the reference lists.

Study selection and assessment of bias risk

Two investigators independently assessed publications considered to be eligible for inclusion at the title and/or abstract level. Full-text reviews were conducted if it was difficult to ascertain from the abstract whether the article met our inclusion/exclusion criteria. The risk of bias in each study was evaluated by two independent investigators using the Scottish Intercollegiate Guideline Network checklist. The questions posed explored concealment of patient allocation and the presence of other potential sources of bias.

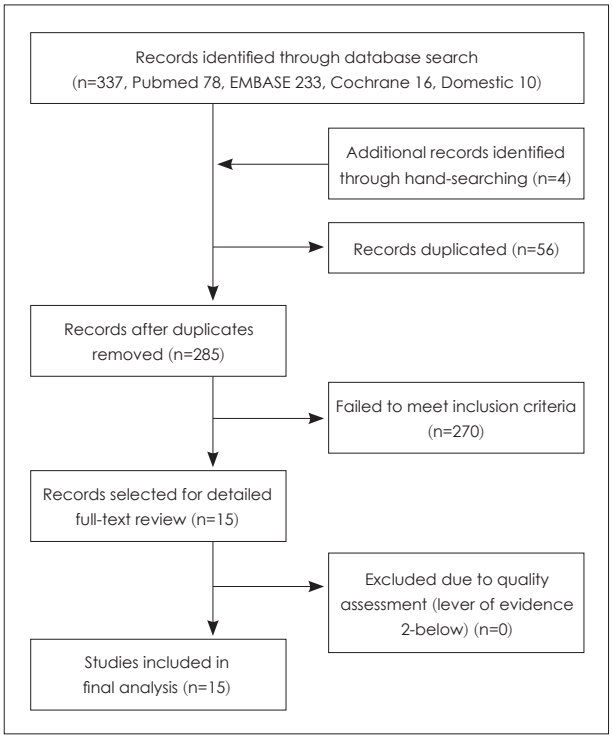

Fig. 1. Flowchart showing search and selection of studies for review.

Data collection and analysis

A standardized data extraction form was used to extract outcomes of interest and two investigators independently extracted data from selected full-text articles using this form (which reinforced the inclusion and exclusion criteria). Outcome variables included procedural, fluoroscopic time, and RF application times, acute success rates upon treatment of patients, AF recurrence, need for repeat procedures and complications, in an effort to evaluate the procedural durability and efficacy of MEA compared to CPVI. If the two reviewers disagreed on any topic, the disagreement was resolved by consultation. We performed a meta-analysis to estimate pooled estimates of standardized mean differences (SMDs) or relative risks (RRs) among outcome variables. Pooled estimates were obtained using fixed-effect or random-effects models, depending on the extent of heterogeneity evident among studies. Heterogeneity was assessed by derivation of Q statistics and quantified using Higgin's I^2 statistic. Also, all of sensitivity analysis, subgroup analysis, and meta-regression were used to assess

Table 1. Characteristics of studies included in the meta-analysis

Study	Country	Study design	No. of patients (MEA/CPVI)	AF type	Age (MEA vs. CPVI)	Follow-up
Steinwender et al.[14]	Austria	Non randomized study	64 (38/26)	Paroxysmal AF	59±10 vs. 60.5±9.1	6 months
Bulava et al.[13]	Czech Republic	RCT	102 (51/51)	Paroxysmal AF	56.5±9.9 vs. 59.8±11.9	200±13 days
Tivig et al.[16]	Switzerland	Non randomized study	420 (209/211)	Paroxysmal/persistent AF	61±10 vs. 58±10	6.7 months
Bittner et al.[17]	Chile	RCT	80 (40/40)	Paroxysmal/persistent AF	57±11 vs. 59±9	254±99 days
Choo et al.[18]	UK	RCT	109 (38/71)	Paroxysmal/persistent AF	56.9±10.2 vs. 58.2±10.0	6 months
Herrera Siklódy et al.[19]	Germany	Non randomized study	51 (24/27)	Paroxysmal/persistent AF	59±10 vs. 61±10	1–2 days
Deneke et al.[20]	Germany	Non randomized study	14 (11/3)	Paroxysmal/persistent AF	61±8	6.2 months
Gaita et al.[21]	Italy	RCT	72 (36/36)	Paroxysmal AF	57±9 vs. 57±7	1–2 days
Khaykin et al.[10]	Canada	Non randomized study	50 (31/19)	Paroxysmal AF	63±10 vs. 57±12	12 months
Beukema et al.[22]	The Netherlands	Non randomized study	185 (89/96)	Paroxysmal AF	55.9±9.9 vs. 56.0±10.4	363.98±138.65 days
Bulava and Hanis[23]	Czech Republic	Non randomized study	237 (79/158)	Paroxysmal AF	59±10 vs. 58±9.5	24 months
De Greef et al.[24]	Belgium	RCT	161 (79/82)	Paroxysmal/persistent AF	60±10 vs. 58±10	3 years
Gal et al.[25]	The Netherlands	RCT	460 (230/230)	Paroxysmal/persistent AF	56.6±10.3 vs. 56.1±9.8	43 months
McCready et al.[26]	UK	RCT	188 (94/94)	Paroxysmal AF	58±12 vs. 62±11	12 months
Spitzer et al.[27]	Germany	Non randomized study	539 (388/151)	Paroxysmal/persistent AF	61.7±9.7 vs. 58.1±9.3	24 months

AF: atrial fibrillation, MEA: multielectrode catheter ablation, CPVI: conventional pulmonary vein isolation, RCT: Randomized Controlled Trial

heterogeneity. Forest plots and pooled estimates were produced using Review Manager version 5.2 (the Cochrane Collaboration). Funnel plot and meta-regression analysis were performed with the aid of Stata version 12.0 (Stata Corporation, College Station, TX, USA).

Results

Literature search and study characteristics

Of the 337 articles reviewed, 15 including 2732 patients satisfied our predetermined inclusion criteria;[10,14-27] these included seven randomized controlled trials[15,17,18,21,24-26] and eight non-randomized comparative studies[10,14,16,19,20,22,23,27] (Fig. 1). Study characteristics are listed in Table 1. Overall, 1437 patients underwent MEA procedures, and 1295 patients CPVI, to treat paroxysmal or persistent AF. Of the 15 selected studies, 7 dealt with paroxysmal AF patients and 8 included those with paroxysmal or persistent AF.

Procedural outcomes

Procedural and fluoroscopic times

The total MEA procedural time was 45 min less than that of CPVI [SMD=-1.17, 95% confidence interval (CI): -1.67, -0.67, p<0.00001] (Fig. 2). The total fluoroscopic time was also significantly less (by 7.16 min) when MEA rather than CPVI was performed (SMD=-0.64, 95% CI: -1.04, -0.24, p=0.002). The MEA RF application time was 11.96 min shorter than that associated with CPVI, and this difference was significant (SMD=-0.70, 95% CI: -1.26, -0.14, p=0.01).

Table 2 shows our subgroup analysis of the pooled estimates of SMDs in procedural time between MEA and CPVI stratified by study design, AF type, and catheter type. In terms of study design, the MEA procedural time was significantly less than that of CPVI in both randomized (SMD=-1.17, 95% CI: -1.63, -0.71, p<0.00001) and non-randomized controlled trials (SMD=-1.16, 95% CI: -2.07, -0.25, p=0.01), and the pooled SMD was larger for Randomized Controlled Trials. In terms of AF type, MEA was associated with a procedural time significantly shorter than required for CPVI (SMD=-0.97, 95% CI: -1.54, -0.40, p=0.0009) in patients with paroxysmal AF, but not in those with persistent AF (SMD=0.24, 95% CI: -0.12, 0.60, p=0.19). The MEA procedural time was significantly shorter than that of CPVI when either catheter type was used for multielectrode ablation. The catheters used were a duty-cycled multipolar ablation catheter (SMD=-1.15, 95% CI: -1.67, -0.62, p<0.0001) and a high-density mesh ablator catheter (SMD= -1.54, 95% CI: -2.11, -0.97, p<0.00001).

Clinical outcomes

Ten studies[10,14-19,21-23] reported the success rates of acute procedures in terms of complete PV isolation immediately after ablation. No significant between-treatment difference in acute procedural success rate was evident (RR=0.99, 95% CI: 0.97, 1.01, p=0.35). After ablation, the risk of AF recurrence was lower if MEA had been employed (RR=0.85, 95% CI: 0.76, 0.94, p=0.002) (Fig. 3) with statistical significance from twelve studies[10,14-18,22-27] reporting AF recurrence. Also, the number of repeat procedures performed after initial ablation that did not completely isolate the PV was somewhat less after MEA than CPVI (RR=0.73, 95% CI: 0.53, 1.00, p=0.05), but the difference was not significant.

Table 3 presents our subgroup analysis results for AF recurrence stratified by follow-up period, study design, AF type, and catheter type used during MEA. AF recurred less often after MEA in studies with shorter follow-up durations (less than 6 months; RR=0.69, 95% CI: 0.45, 1.06, p=0.09, and 6–12 months; RR=0.80, 95% CI: 0.53, 1.19, p=0.27). Also, MEA was associated with a reduced AF recurrence more than 1 year after the procedure (RR=0.87, 95% CI: 0.78, 0.97, p=0.01) and the difference was statistically significant. Meta-regression of the RRs for AF recurrence after MEA vs. CPVI in terms of follow-up duration showed a tendency toward establishment of a slightly positive linear relationship between the RR and follow-up duration without significance (β=0.005, 95% CI: -0.007, 0.017, p=0.395) (Fig. 4).

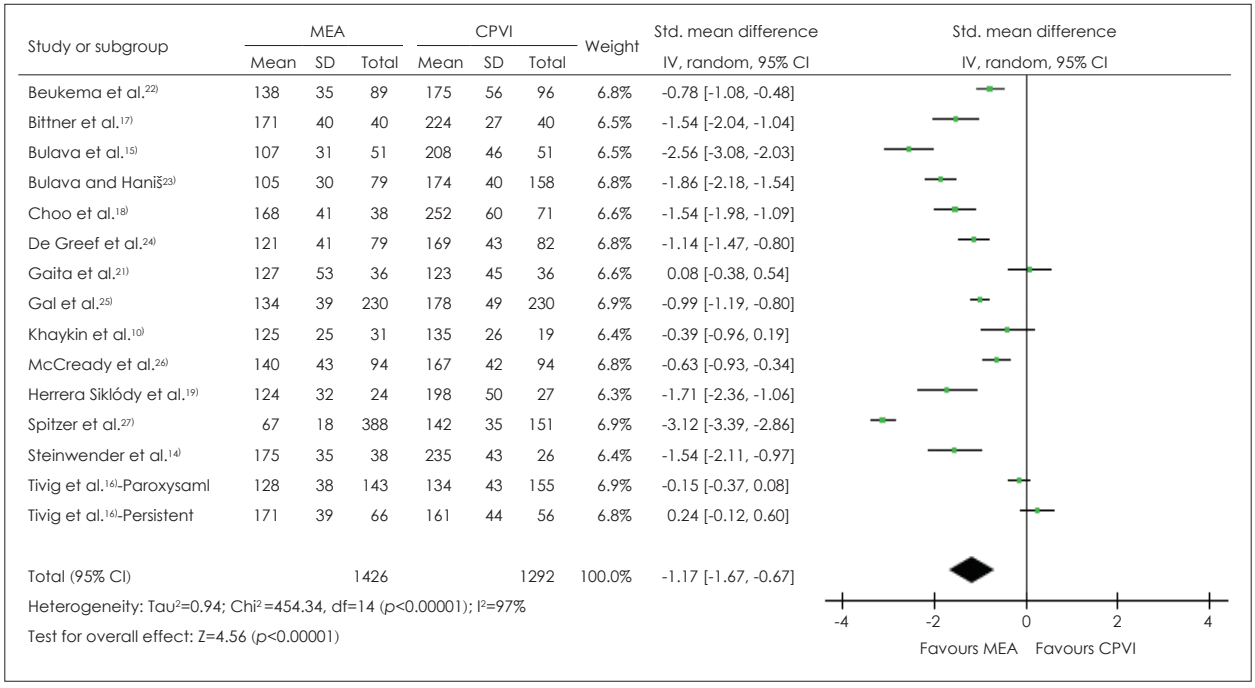

Fig. 2. Forest plot for standardized mean difference (SMD) for procedure time between multielectrode catheter ablation (MEA) and conventional pulmonary vein isolation (CPVI). CI: confidence interval, SD: standard deviation.

Table 2. Subgroup analysis on the mean difference of procedure time between MEA and CPVI

Sub-group		No. of study	No. of patients		Std. mean difference (95% CI)
			MEA	CPVI	
Total		14	1426	1292	-1.17 (-1.68, -0.67)*
Sensitivity analysis†		12	1181	1045	-1.48 (-1.98, -0.98)*
Study design	RCT	7	568	604	-1.17 (-1.63, -0.71)*
	Non randomized study	7	858	688	-1.16 (-2.07, -0.25)*
AF type	Paroxysmal AF	8	561	635	-0.97 (-1.54, -0.40)*
	Persistent AF	1	66	56	0.24 (-0.12, 0.60)
Catheter type	Duty-cycled multipolar ablation catheter	14	1388	1266	-1.15 (-1.67, -0.62)*
	High-density mesh ablator catheter	1	38	26	-1.54 (-2.11, -0.97)*

*Pooled estimates are from random-effects model, †Sensitivity analysis was performed by excluding extreme studies. AF: atrial fibrillation, MEA: multielectrode catheter ablation, CPVI: conventional pulmonary vein isolation, CI: confidence interval, RCT: randomized controlled trial

Complications

Reported complications associated with PV isolation via catheter ablation included embolisms, pericardial effusion, stroke, tamponade, pulmonary vein puncture, transient ischemic attack, femoral hematoma, and pseudoaneurysms. No significant between-treatment difference in the frequency of occurrence of any complication was evident, but a trend toward a higher complication rate after MEA was apparent (RR=1.04, 95% CI: 0.55, 1.93, p=0.91) (Fig. 5). Eight studies [17,19-21,24-27] reported thromboembolic complications, the most frequent and potentially devastating. Of eight relevant studies, three[19,21,26] reported thromboembolic events in the first 1–2 days after the procedure and the other five[17,20,24,25,27] gave follow-up results at more than 6 months up to 3 years. The risk of thromboembolic events tended to be slightly lower after MEA (RR=0.99, 95% CI: 0.23, 4.19, p=0.99) at follow-up times of over 6 months, in contrast to a higher incidence (RR=4.84, 95% CI: 2.04, 11.47, p=0.0003) observed during the acute period (1–2 days after the procedure) (Supplementary Fig. 1).

Discussion

Our present systematic review and meta-analysis found that RF ablation using multielectrode catheters reduced procedural

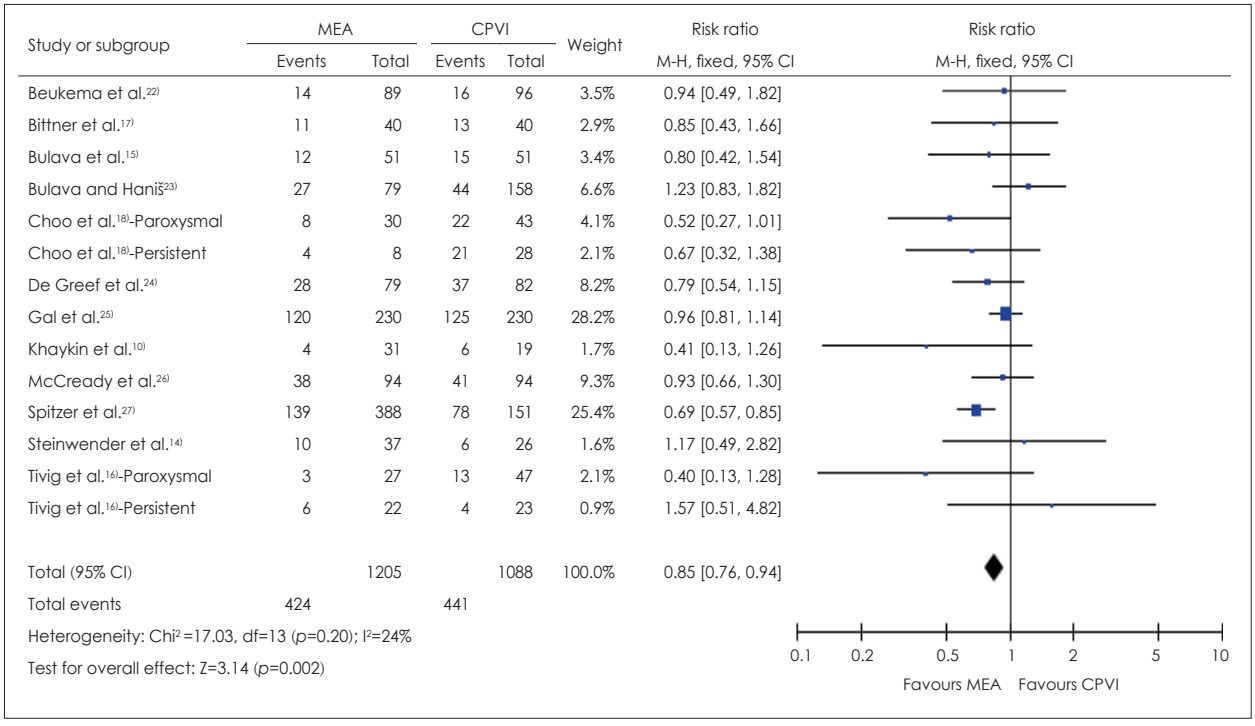

Fig. 3. Forest plot for relative risk (RR) of AF recurrence between multielectrode catheter ablation (MEA) and conventional pulmonary vein isolation (CPVI). CI: confidence interval.

Table 3. Subgroup analysis on the RRs of AF recurrence between MEA and CPVI

Sub-group		No. of study	No. of patients		RR (95% CI)†
			MEA	CPVI	
Total		14	1205	1088	0.85 (0.76, 0.94)
Follow-up period	≤6 month	3	75	97	0.69 (0.45, 1.06)
	>6 month, <1 year	4	140	161	0.80 (0.53, 1.19)
	≥1 year	7	990	830	0.87 (0.78, 0.97)*
Study design	RCT	7	532	568	0.87 (0.77, 1.00)
	Non randomized study	7	673	520	0.81 (0.68, 0.96)*
AF type	Paroxysmal AF	8	438	534	0.88 (0.72, 1.07)
	Persistent AF	2	30	51	0.93 (0.51, 1.72)
Catheter type	Duty-cycled multipolar ablation catheter	13	1168	1062	0.84 (0.76, 0.93)*
	High-density mesh ablator catheter	1	37	26	1.17 (0.49, 2.82)

*Statistically significant, †Mantel-Haenszel pooled estimate. AF: atrial fibrillation, MEA: multielectrode catheter ablation, CPVI: conventional pulmonary vein isolation, RR: relative risk, CI: confidence interval, RCT: Randomized Controlled Trial

times and AF recurrence compared to those of CPVI using 3D mapping, but the overall efficacies were in terms of acute procedural success and the need for repeat procedures were comparable. The procedural time was significantly reduced in the MEA group, but differed among the studies reviewed. Two studies[16,21] reported that MEA procedural time was longer than that of CPVI, contrary to other studies. Perhaps the surgeons performing MEA were at early stages of their learning curves, whereas the surgeons performing CPVI were not. The result has also shown a similarity in fluoroscopy time and RF application time representing longer time in MEA. Some abstracts[28-31] reported that the learning curve for use of multielectrode catheters was relatively short. Over the first 20 cases, procedural, fluoroscopic, and application times decreased by 33%, 45%, and 21%, respectively; and acute success rates increased with procedure experience. Subgroup analysis by AF type showed that all of procedural, fluoroscopic, and RF application times during treatment of paroxysmal AF patients were shorter when MEA was applied, but, in contrast, procedural times for persistent AF patients were longer. Such differences between AF type may be attributable to the need to perform additional ablation dictated by complex fractionated atrial electrograms obtained from the left atrial septum and body, performed at the discretion of the operator in patients with persistent AF.

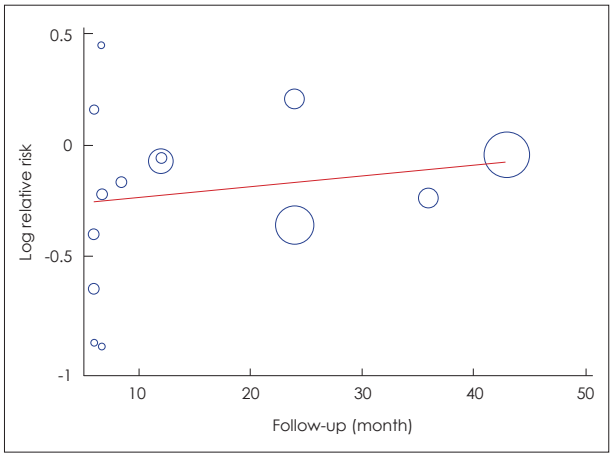

Fig. 4. Meta-regression for relative risk of AF recurrence on follow-up duration in the study. AF: atrial fibrillation.

The acute success rates were comparably high between treatments, being 82−100% in most studies when either MEA or CPVI was employed. However, the acute success rate of 79−93% for persistent AF patients was slightly lower than that for paroxysmal AF patients, attributable to the need for additional ablation to treat persistent AF, as mentioned above.

The RRs of AF recurrence after MEA and CPVI varied by follow-up period, and tended to be lower short-term (≤1 year) after MEA, and the difference was significant between MEA and CPVI upon longer-term follow-up (>1 year); this tendency was also captured via meta-regression analysis. Likewise, the risk of a need for a repeat procedure was lower after MEA than CPVI. Such a finding was expected because the need for

Study or subgroup	MEA Events	MEA Total	CPVI Events	CPVI Total	Weight	Risk ratio M-H, random, 95% CI
Beukema et al.[22]	3	89	2	96	7.3%	1.62 [0.28, 9.46]
Bittner et al.[17]	1	40	2	40	5.0%	0.50 [0.05, 5.30]
Bulava et al.[15]	0	51	0	51		Not estimable
Bulava and Haniš[23]	2	79	11	158	8.9%	0.36 [0.08, 1.60]
Choo et al.[18]-Combined	2	38	2	71	6.6%	1.87 [0.27, 12.74]
De Greef et al.[24]	4	79	5	82	10.2%	0.83 [0.23, 2.98]
Deneke et al.[20]	2	11	1	3	6.2%	0.55 [0.07, 4.16]
Gaita et al.[21]	14	36	3	36	11.0%	4.67 [1.47, 14.86]
Gal et al.[25]	3	230	11	230	10.3%	0.27 [0.08, 0.96]
McCready et al.[26]	2	94	0	94	3.4%	5.00 [0.24, 102.77]
Herrera Siklódy et al.[19]	9	24	2	27	9.2%	5.06 [1.21, 21.16]
Spitzer et al.[27]	6	388	5	151	10.9%	0.47 [0.14, 1.51]
Tivig et al.[16]	5	209	6	211	10.9%	0.84 [0.26, 2.71]
Total (95% CI)		1368		1250	100.0%	1.04 [0.55, 1.93]
Total events	53		50			

Heterogeneity: Tau²=0.57; Chi²=21.86, df=11 (p<0.03); I²=50%

Test for overall effect: Z=0.11 (p=0.91)

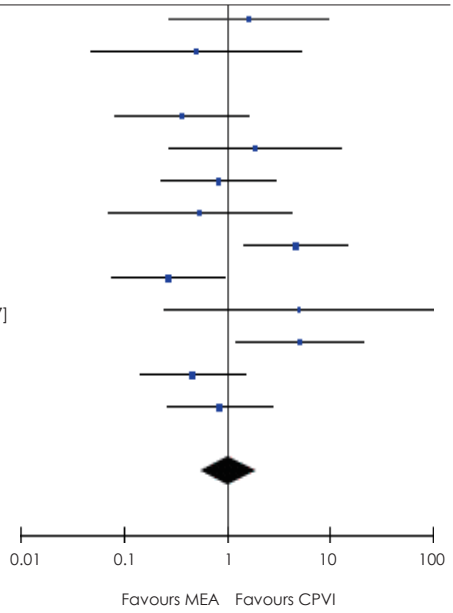

Fig. 5. Forest plot for the pooled RR of complications between multielectrode catheter ablation (MEA) and conventional pulmonary vein isolation (CPVI). RR: relative risk, CI: confidence interval.

a repeat procedure is triggered by AF recurrence, which is more common after CPVI. Tivig et al.[16] reported that low-power MEA ablation reduced the need for repeat procedures compared to use of standard RF ablation; low-power ablation to a defined lesional depth (using appropriate generator settings) may prevent extensive tissue injury. The success of MEA is explained by the high-level lesional integrity afforded by use of circumferential ablation catheters compared to the point-by-point ablation of 3D systems. Improved lesional integrity reduces the opportunities for reconnection of trigger foci. Although 3D systems allow precise visualization of the positions of mapping and ablation catheters, construction of such complex maps is associated with a steep learning curve, compromising success rates in newer centers.

Of the various complications associated with the MEA and CPVI procedures, thromboembolic events were the most common and the risk of such events was somewhat higher after MEA, significantly different from the risk after CPVI. However, sub-group analysis by follow-up period revealed that the risk of such events tended to be slightly lower upon longer-term follow-up after MEA, in contrast to the higher incidence observed during the acute period (1−2 days) after the procedure. Deneke et al.[20] evaluated the clinical consequences and longer-term characteristics of lesions in patients with acutely detected ischemic embolic lesions after catheter ablation of AF. Only acute lesions of maximum diameters >10 mm were detected on longer-term follow-up MRI; 94% of lesions resolved without identifiable scar formation. The mechanisms by which silent brain injuries are caused remain unclear; blood clots, air, tissue, or fat, may be in play. Alternatively, such injuries may be produced upon sheath manipulation prior to left atrial catheterization, or by ablation per se. Asymptomatic cerebral MRI lesions may trigger subclinical deterioration, but no patient had any detectable neurological deficit immediately after ablation or on follow-up evaluation performed by an experienced neurologist.[20] Also, no AF ablation study revealed any connection between development of silent ischemic MRI lesions and adverse neuropsychological outcomes.[32,33] Although the development of thromboembolic events after AF ablation is of concern, no relationship between such events and an adverse outcome or deterioration in neuropsychological performance was substantiated in any trial. Further long-term studies are needed to evaluate patient outcomes. The catheter type used during MEA was associated with development of thromboembolic events. Recently, Verma et al.[34] described several ways by which the development of silent intracranial embolisms may be minimized via catheter manipulation and appropriate electrode use with maintenance of good success rates.

Conclusions

Upon meta-analysis, multielectrode ablation used to treat AF afforded beneficial reductions in all of procedural, fluoroscopic, and RF application times, but the outcomes in terms of acute procedural success, AF recurrence and the need for repeat procedure were comparable to those of traditional treatment, CPVI. Although the thromboembolism risk at 1−2 days post-procedure was slightly elevated, the long-term safety profile of MEA was comparable to that of CPVI, indicating that MEA benefits patients with AF when skilled physicians perform the procedure carefully. Further, larger, well-organized randomized trials combined with analysis of cost-effectiveness are needed.

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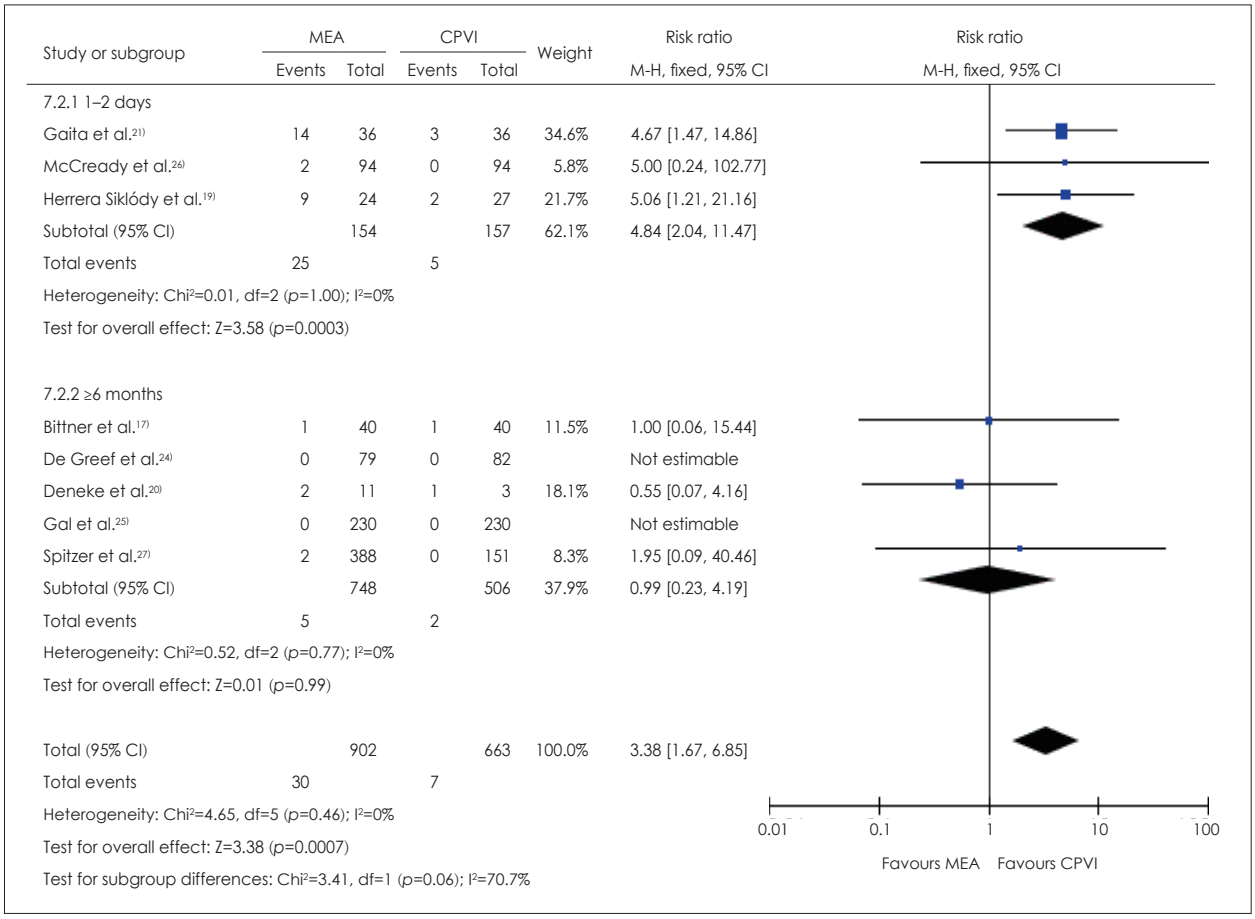

Supplementary Fig. 1. Forest plot for stratified relative risks (RR) of thromboembolic events between multielectrode catheter ablation (MEA) and conventional pulmonary vein isolation (CPVI) by follow-up duration. CI: confidence interval.